

Part VI: Summary of the risk management plan by product

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Attention-Deficit/Hyperactivity Disorder (ADHD)

The occurrence of ADHD in children appears to be 3-7%, of which 30-80% may have the disorder as adults¹. The existing data suggest that the occurrence of ADHD is approximately 4 % in the adult population.⁴ ADHD is associated with other important psychiatric concomitant diseases. People with ADHD have been identified in every country studied, with similar frequencies. ADHD is more frequently diagnosed in boys than in girls. The likely outcome of the disorder for patients with ADHD is excellent if the patient has no major other disorders/diseases and the medication is correctly adapted to patient's concomitant disorders/diseases. Other important factors influencing the outcome are an appropriate education about ADHD for patients and caregivers and coexistence of learning difficulties and emotional problems to be investigated and treated appropriately¹. Atomoxetine is used only as a part of the total treatment of the disorder which also requires treatments which do not involve medicines, such as counselling and behavioural therapy.

VI.2.2 Summary of treatment benefits

Attention-Deficit/Hyperactivity Disorder (ADHD)^{1,2,3}

The two major components in the medical care of children with ADHD, are behavioral and pharmaceutical therapies. Behavioral therapy often is effective when used in combination with medication. The symptoms may decrease with age because of a better self-control and changes in brain composition that occur during late adolescence.¹

Pharmacological treatment is not indicated in all patients with this syndrome and the decision to use the drug must be based on a very thorough assessment of the severity of the patient's symptoms and impairment in relation to the patient's age and the persistence of symptoms.³ Two studies showing the success of atomoxetine in the treatment of ADHD are presented below ².

One study performed on 171 children and adolescents aged 6 to 16 years old were assigned by chance to receive 6 weeks of treatment with either atomoxetine (ATX) (administered once daily) or placebo (a substance having no pharmacological effect). The doses were increased from 0.5 mg/kg/day to 1.0 mg/kg/day and to 1.5mg/kg/day for patients having still a high severity score. The conclusion was that once-daily administration of ATX is a helpful treatment for children and adolescents with ADHD.

A study was performed on 502 ADHD adult patients that were assigned to receive by chance either atomoxetine (n=234) or placebo (n=268) for 24 weeks following 2-weeks of usually recommended doses (40 mg for 3 days than 80 mg) or slower increase of doses (40 mg for 7 days than 80 mg). After 24 weeks, placebo patients received atomoxetine in one of two schemes. Different scales that were used for measuring the effectiveness showed a significant improvement in ADHD symptoms at 12 and 24 weeks over placebo. Adverse events overall and for usual recommended doses or slow increase of doses to ATX were similar and consistent with previous adult ATX studies.

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about success of atomoxetine in the target population (children over six years of age, young people and adults) were identified, that would warrant post-authorisation effectiveness studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, taking into account factors such as age, sex, race or organ impairment.

The long-term data is limited and therefore, patients requiring long-term therapy should be carefully monitored. In addition, re-evaluation of the need for continued therapy beyond 1 year should be performed, particularly when the patient has reached a stable and satisfactory response.

In addition, for elderly patients the use of atomoxetine has not been systematically evaluated.

Moreover, clinical data on exposed pregnancies are limited and insufficient to allow for an association or a lack of association between atomoxetine and adverse pregnancy and/or lactation outcomes.

However, there is no evidence to suggest that treatment results would be different for these patient groups.

VI.2.4 Summary of safety concerns:**Important identified risks**

Risk	What is known	Preventability
Thoughts or an unusual preoccupation with killing oneself (Suicidal Ideation)	Thoughts or an unusual preoccupation with killing oneself has been reported in patients treated with atomoxetine. In studies, unusual preoccupation with killing oneself were uncommon but more frequently observed among children and adolescents treated with atomoxetine compared to those treated with placebo (a substance having no pharmacological effect), where there were no events, while in adults there was no difference.	Patients who are being treated for ADHD should be carefully monitored of unusual preoccupation of killing oneself that may first appear or worsen.
Liver problems (Hepatic injury)	Very rarely, spontaneous reports of liver problems, manifested by increase of blood tests that detect inflammation and damage to the liver with having yellow skin or yellow eyes (jaundice), have been reported. Also very rarely, severe liver injury, including acute liver failure, has been reported. Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted.	Yes, by monitoring for early symptoms.
Increased blood pressure and increased heart rate	Atomoxetine can affect heart rate and blood pressure. Most patients taking atomoxetine experience a modest increase in heart rate (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg).	Prior to prescribing it is necessary to take an appropriate medical history and physical exam and evaluate patient's heart status, including blood pres-

Risk	What is known	Preventability
	<p>However, some ADHD studies show that approximately 8-12% of children and adolescents, and 6-10% adults experience more pronounced changes in heart rate (20 beats per minute or greater) and blood pressure (15-20 mmHg or greater). Analysis of these studies showed that approximately 15-26% of children and adolescents, and 27-32% of adults experiencing such changes in blood pressure and heart rate during atomoxetine treatment had sustained or progressive increases. Long-term sustained changes in blood pressure may potentially contribute to complications like thickening of the heart muscle (myocardial hypertrophy).</p> <p>Salbutamol (a medicine to treat asthma) when taken concomitantly with atomoxetine, by mouth or injected may make the patient feel as if the heart is racing, but this will not make the asthma worse.</p>	<p>sure and heart rate. Ongoing monitoring is also recommended for blood pressure and pulse recorded after each adjustment of dose and then at least every 6 months. For paediatric patients the use of a centile chart is recommended. For adults, current reference guidelines for high blood pressure should be followed.</p> <p>Atomoxetine should not be used in patients with severe disease affecting the heart and/or blood vessels (cardiovascular disease) or stroke. Atomoxetine should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure and heart rate, such as patients with increased blood pressure, increased heartbeat, cardiovascular disease or past medical history of stroke.</p>
Poor blood circulation which makes toes and fingers numb and pale (Peripheral vascular instability (Raynaud's phenomenon))	In studies and post-marketing, poor blood circulation which makes toes and fingers numb and pale (Raynaud's phenomenon) was rarely reported in children, adolescents and adults.	Yes, by monitoring for early symptoms.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Heart, vessels and brain effects <ul style="list-style-type: none"> • heart rhythm disorder that can potentially cause fast, chaotic heartbeats 	There are underlying medical conditions that could be worsened by increases in blood pressure and heart rate, such as in patients with previously diagnosed high blood pressure or faster heart beat, diseases related to blood vessels or brain diseases. Patients who develop symptoms such as palpitations (sensation of rapid, irregular, or forceful heartbeats), chest pain, unex-

Risk	What is known (Including reason why it is considered a potential risk)
(QTc prolongation) <ul style="list-style-type: none"> • condition of insufficient blood flow to the heart muscle via the coronary arteries, often resulting in chest pain (Myocardial ischaemia) • Very fast heartbeat (Tachyarrhythmia) • Stroke (Cerebrovascular accident) 	<p>plained fainting, shortness of breath or other symptoms suggestive of heart disease during atomoxetine treatment should undergo a prompt specialist heart evaluation.</p> <p>Patients with additional risk factors for brain and blood vessels conditions (such as a history of heart and vascular disease, concomitant medications that increase blood pressure) should be assessed at every visit for signs and symptoms of nervous systems after initiating treatment with atomoxetine.</p> <p>In addition, atomoxetine should be used with caution in patients with inherited or acquired long QT or a family history of QT prolongation.</p> <p>Patients, who have serious problems with the heart which may be affected by an increase in heart rate and/or blood pressure, cannot take atomoxetine. If the patient has serious problems with the blood vessels in the brain - such as a stroke, swelling and weakening of part of a blood vessel (aneurysm) or narrow or blocked blood vessels or have a tumour of adrenal gland (phaeochromocytoma) cannot use atomoxetine.</p>
Feeling aggressive, unfriendly and angry (Aggression/hostility)	<p>Feeling aggressive, unfriendly and angry were more frequently observed in studies among children, adolescents and adults treated with atomoxetine compared to those treated with placebo (substance having no pharmacological effect). Emotional lability was more frequently observed in studies among children treated with atomoxetine compared to those treated with placebo. Patients should be closely monitored for the appearance or worsening of aggressive behaviour, hostility or emotional lability.</p>
Seizures	<p>Seizures are a potential risk with atomoxetine. Atomoxetine should be introduced with caution in patients with a history of seizure. Discontinuation of atomoxetine should be considered in any patient developing a seizure or if there is an increase in seizure frequency where no other cause is identified.</p> <p>Caution is advised with concomitant use of medicinal drugs which are known to increase the risk of seizures.</p>

Missing information

Risk	What is known
NA	NA

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Increased blood pressure and increased heart rate

Healthcare Professional education
<p><u>Objective and rationale:</u> To reinforce the warnings regarding the associated risk of increased heart rate and increased blood pressure associated with atomoxetine, the cardiovascular or cerebrovascular disorder contraindication and the recommendation to monitor blood pressure and heart rate in all patients before and during treatment. To ensure prescribers are fully aware of the appropriate manner of prescribing atomoxetine.</p>
<p><u>Proposed action:</u> All atomoxetine prescribers (e.g. psychiatrists) will receive sufficient number of Prescriber Packs. Prescriber Pack includes: Introductory Cover Letter A copy of the SmPC Physician's Guide including additional tools: Checklist for actions to take before prescribing / dispensing or administering atomoxetine Checklist for monitoring to manage cardiovascular risks with atomoxetine treatment Measurements recording chart</p>

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for atomoxetine.

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 1. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	19-02-2015	<p><u>Identified Risks</u> Suicidal Ideation Hepatic injury Increased blood pressure and increased heart rate</p> <p><u>Potential Risks</u> Peripheral vascular instability (Raynaud's phenomenon)</p>	First version

Version	Date	Safety Concerns	Comment
		Cardiovascular and cerebrovascular outcomes <ul style="list-style-type: none">• QTc prolongation• Myocardial ischaemia• Tachyarrhythmia• Cerebrovascular accident Aggression/hostility Seizures	
2.0	23-07-2015	The risks are not changed.	The targeted follow-up forms were added.
2.1	18-12-2015	The risks are not changed.	Minor changes in Part VI

